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Selective palladium(II)-mediated oxidation of homoallylic *N-tert*-butanesulfinyl amine derivatives†

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The palladium(II)-catalyzed oxidation of homoallylic amine derivatives resulting from the allylation of *N-tert*-butanesulfinyl imines with allyl bromide, led to the formation of the corresponding terminal allylic acetates in a regioselective fashion in moderate yields. In the case of the homoallylic amine derivatives obtained using cyclohexenyl bromide as allylating reagent, the allylic oxidation took place with high regio- and diastereoselectivity and yields ranging from 40 to 85%.

Alkenes are easily available compounds from different sources and are also the starting reagents in many multy-step syntheses of complex organic molecules. For that reason, methodologies for alkene functionalization at an allylic position through C-H activation[1] are of great interest. Considering atom economy, C-H activation is superior to other strategies such as, for instance, nucleophilic substitution on substrates bearing a leaving group. Among these methodologies, the allylic oxidation was first achieved using organic peroxides in the presence of catalytic amounts of copper (Kharasch-Sosnovski reaction),[2] or by means of stoichiometric amounts of highly toxic chromium(VI) salts[3] or selenium dioxide.[4] Palladium(II) compounds were also effective in these transformations, the stoichiometric version reported almost simultaneously by Moiseev[5] and Winstein[6] in the early 1960s. Later, it was found that a catalytic amount of a palladium(II) salt in the presence of excess of oxidants, such as manganese, 1,4-benzoquinone (BQ) or oxygen[7] worked equally well for the allylic oxidation. In general the reactions were extremely substrate dependent, being difficult to control both the regiochemistry and the stereochemistry of the process.[8] More recently, ligands and conditions were reported for carrying out efficient methods to perform allylic oxidations in a regioselective manner,[9] White catalyst **1** was found to be especially successful in these transformations, leading almost exclusively to the branched products (Scheme 1A).[10] Stereoselective allylic oxidations were also achieved performing the oxidation with **1** in combination with a chromium(III)-salen complex.[11] In all cases, the presence of functional groups could facilitate the control of the regiochemistry and the sterochemistry of the allylic oxidations when the functional group was involved in an intramolecular process.[12] On the other hand, we have described the stereoselective synthesis of *N-tert*-butanesulfinyl homoallylic amines through an indium mediated allylation of the corresponding imines with allylic bromides[13] or alcohols.[14] The corresponding homopropargylic derivatives have also been prepared using trimethylsilylpropargyl bromide.[15] All these compounds have been used as precursors in the synthesis of natural products[16] and other enantioenriched nitrogen containing heterocycles.[17] Continuing our interest in this topic, we herein report our first approach to the palladium(II)-catalyzed oxidation of *N-tert*-butanesulfinyl homoallyl amine derivatives, in order to determine the influence of the *tert*-butanesulfinamide group in the regio and stereoselectivity of the process. To the best of our knowledge, the only example of a palladium(II)-catalyzed oxidation of an alkene bearing a *tert*-butanesulfinamide group was reported by Stahl,[18] furnishing 2,5-disubstituted pyrrolidines, through nucleophilic addition of the nitrogen of the sulfonamide group to the π-allyl palladium(II) cationic intermediate initially formed (Scheme 1B).

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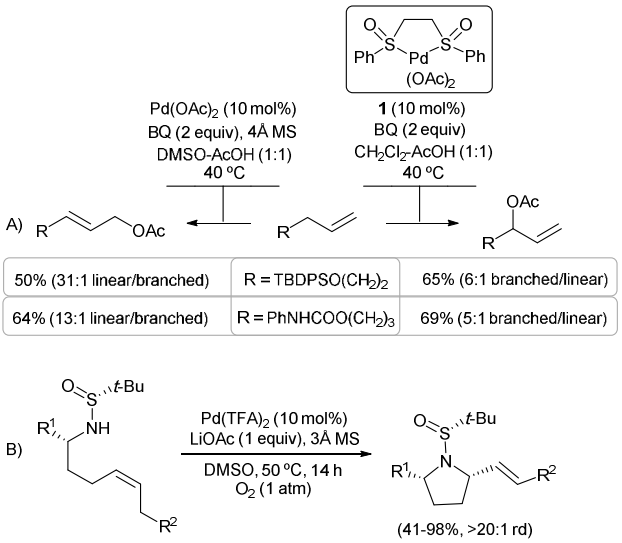
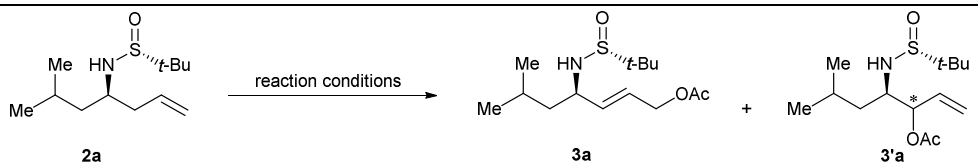


Scheme 1 Examples of regioselective allylic functionalization of alkenes

The chiral *N*-*tert*-butanesulfinyl homoallyl amine derivative **2a** (easily prepared by allylation of the corresponding imine)[13] was taken as the model substrate for the optimization of the reaction conditions in the palladium(II)-catalyzed oxidation. Thus, low conversion (10%) and formation exclusively of the linear oxidized reaction product **3a** was observed under the reaction conditions developed by White[10] which were found to be optimal for the formation of branched products (e. g. 3'a; Table 1, entry 1). Conversions and yields were even lower when $Pd(OAC)_2$ and $Pd(TFA)_2$ were used as palladium source, instead of White catalyst **1**, under the same reaction conditions (Table 1, entries 2 and 3, respectively). None of the expected allylic oxidized products were formed when trifluoroacetic acid (TFA) was used instead of acetic acid in the presence of both White catalyst **1** and $Pd(TFA)_2$ (Table1, entries 4 and 5). On the other hand, switching from *p*-benzoquinone (BQ) to methyl-*p*-benzoquinone (MEBQ) led to a similar result to those found in entries 1-4 (Table 1, entry 6). Fortunately, the linear oxidized product **3a** was obtained in 49% yield after column chromatography purification when the reaction was performed in a 1:1 mixture of acetic acid and DMSO, in the presence of 10 mol% of $Pd(OAC)_2$, 2 equivalents of BQ and 3Å molecular sieves at 40 °C (Table 1, entry 7). These conditions were described to led predominantly to the linear isomer in terminal alkenes.[10] Finally, the combination of **1** and BQ in a 1:1 mixture of acetic acid and dichloromethane led to the linear product **3a** although in lower yield than using the acetic acid and DMSO mixture (Table 1, entry 8). We studied next the scope of the oxidation of these homoallyl amine derivatives **2** by applying the optimized conditions depicted in Table 1, entry 7. The expected linear oxidized products **3** were obtained in moderate yields for all the substrates, independently of the structure of homoallyl amine derivatives **2**, which had been prepared starting from chiral aliphatic (**2a** and **2b**) and aromatic (**2c**) aldimines, as well as the ketimine derived from butanone (**2d**) (Table 2).

Surprisingly, allylic oxidation of *N*-*tert*-butanesulfinyl homoallyl amine derivatives of type **4**, which were easily accessible from the corresponding imine and 3-bromocyclohexene through and indium-mediated diastereoselective allylation,[13b] worked well in dioxane with both catalyst **1** and $Pd(OAc)_2$ under the reaction conditions depicted in entries 1 and 2 of Table 1. Allylic oxidation of compounds **4** produced necessarily a new stereogenic center, leading to compounds **5** in a highly regio- and stereoselectivity manner (Table 3). The site oxidation was determined by COSY experiments and the configuration of the newly created stereogenic center in compound **5f** (Table 3) was unambiguously assigned to be *R* after X-ray analysis (see Electronic Supplementary Information).[19] We assumed the same configuration for the rest of compounds **5**, since the allylic oxidation follows a similar pathway.

Table 1 Optimization of the reaction conditions[a]



Entry	Reaction conditions	Conversion (%)[b]	**2a**/**3a**/**3'a** ratio[c]
1	**1** (10 mol%), BQ (2 equiv), AcOH (4 equiv), 1,4-dioxane, 50 °C, 48 h	10	91/9/0
2	$Pd(OAc)_2$ (10 mol%), BQ (2 equiv), AcOH (4 equiv), 1,4-dioxane, 50 °C, 48 h	7	96/4/0
3	$Pd(TFA)_2$ (10 mol%), BQ (2 equiv), AcOH (4 equiv), 1,4-dioxane, 50 °C, 48 h	5	97/3/0
4	**1** (10 mol%), BQ (2 equiv), TFA (4 equiv), 1,4-dioxane, 50 °C, 48 h	100	--[d]
5	$Pd(TFA)_2$ (10 mol%), BQ (2 equiv), TFA (4 equiv), 1,4-dioxane, 50 °C. 48 h	100	--[d]
6	$Pd(OAc)_2$ (10 mol%), MEBQ (2 equiv), AcOH (4 equiv), 1,4-dioxane, 50 °C, 48 h	13	94/6/0
7	$Pd(OAc)_2$ (10 mol%), BQ (2 equiv), 3Å MS, AcOH:DMSO (1:1), 40 °C, 48 h	67	33/67 (49)[e]/0
8	**1** (10 mol%), BQ (2 equiv), AcOH:CH_2Cl_2 (1:1), 40 °C, 48 h	12	84/16/0

[a] Reactions were carried out with 0.2 mmol of **2a**. [b] Conversion is given based on the disappearance of the starting **2a** by ^{1}H NMR. [c] Ratio was determined from ^{1}H NMR spectrum of the crude reaction mixture. [d] Total decomposition of the **2a** took place, the expected allylic oxidized products being not observed. [e] Isolated yield of **3a** is given in parenthesis.

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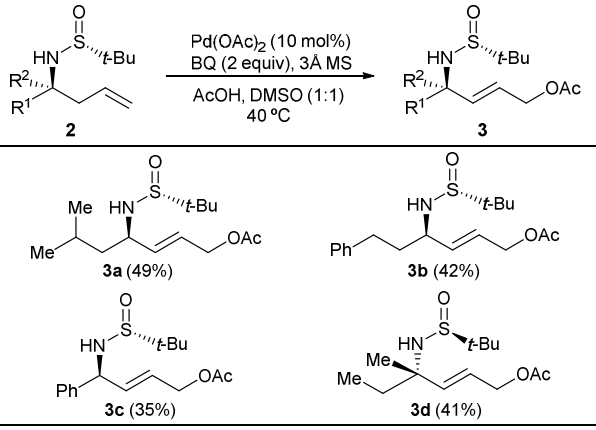
Table 2 Oxidation of chiral homoallyl amine derivatives **2**[a]

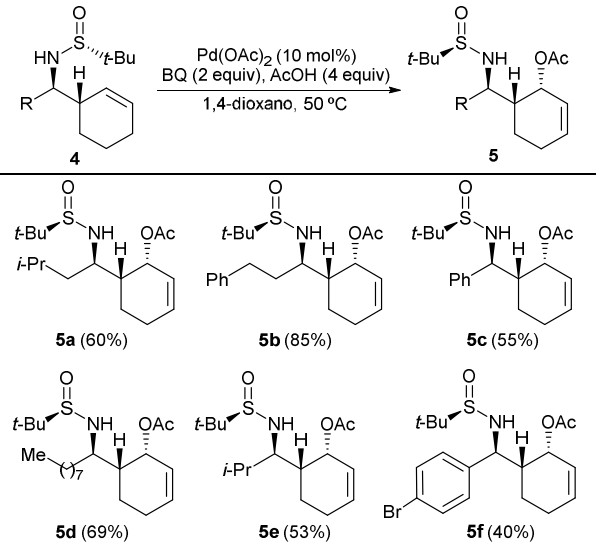


[a] Yields were determined for isolated compounds after column chromatography based on the starting compounds **2**.

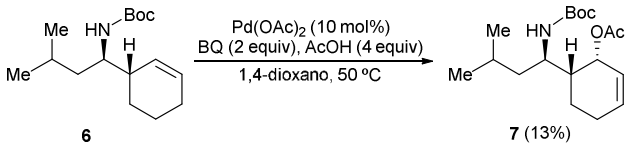
In order to gain insight into the mechanism of this highly regio- and stereoselective process, the influence of the *tert*-butanesulfinamide group was investigated. Thus, *N*-Boc-protected homoallyl amine derivative **6** was prepared from **2a** by removal first of the sulfinyl group under acidic conditions followed by *in situ* treatment with di-*tert*-butyl dicarbonate. Palladium(II)-catalyzed oxidation of **6** led to compound **7** in only 13% yield, meanwhile 67% of the starting compound **6** was recovered after column chromatography purification (Scheme 2). This result clearly indicated the beneficial role of the *tert*-butanesulfinamide group in the outcome of the process if comparing to the *tert*-butoxycarboxamide group.

The oxidation of other structurally related compounds was also investigated. For allylamine

Table 3 Oxidation of chiral homoallyl amine derivatives **4**[a]



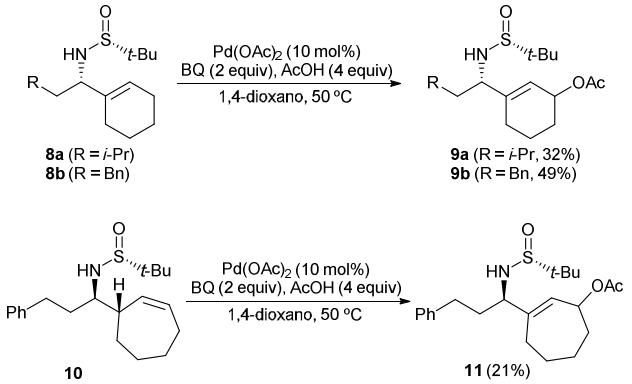
[a] Yields were determined for isolated compounds after column chromatography based on starting compounds **4**.



Scheme 2 Selective allylic oxidation of homoallyl amine derivative **6**

derivatives **8**, prepared by addition of the corresponding organomagnesium compound to the *N*-*tert*-butanesulfinyl imine derived from cyclohexene-1-carbaldehyde,[20] palladium(II) catalyzed oxidation under standard conditions led to compounds **9** in moderate yields (Scheme 3). Importantly, the regiochemistry of the oxidation of homoallylamine derivative **10** was different from that for compounds **4**, yielding in this case compound **11** as the only oxidized reaction product in 21% yield (Scheme 3). The presence of a cycloheptenyl moiety instead of a cyclohexenyl one showed a strong influence in the regiochemical outcome. This is another example of the substrate dependence in these reactions and the difficulty in making predictions. The configuration of the newly created stereogenic center was not determined in these compounds.

A mechanism has been proposed for the palladium(II) catalyzed oxidations of compounds **4**. First a π-allylpalladium complex is formed. Regarding the regiochemistry of the process, two π-allylpalladium complexes are possible: complexes **12** resulting from the abstraction of hydrogen from C-4 and complex **13** which is formed when C-1 hydrogen is involved. Considering reaction products **5**, complex **13** could be discarded. Taking into account the stereochemistry, palladium could be located in both diastereotopic faces of the cyclohexenyl moiety in complex **12** and/or **12'**. Formation of compounds **5** can be explained through a reductive elimination in complex **12'**, involving an acetate group (L = OAc), or more likely, by nucleophilic attack at C-2 of an outer sphere acetate to the π-allyl complex **12**. Palladium(II) is reduced to palladium(0) and it should be reoxidized with stoichiometric amounts of *p*-benzoquinone in order to generate the active catalytic species (Scheme 4).



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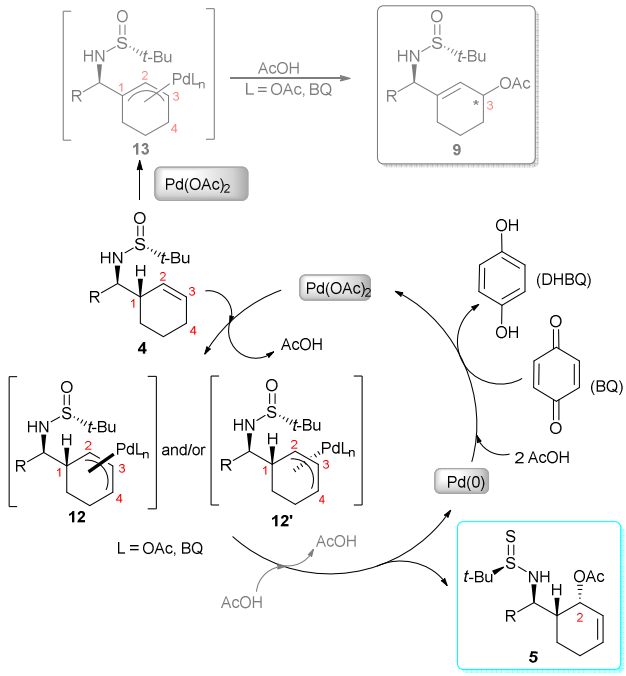
Scheme 3 Selective allylic oxidation of sulfinamides **8** and **10**



Scheme 4 Proposed reaction mechanism

In summary, palladium(II) catalyzed allylic oxidation of easily accessible *N-tert*-butanesulfinyl homoallyl amine derivatives was found to be substrate dependent and took place with high regioselectivity. Linear oxidized products were exclusively obtained in moderate yields from compounds **2** with terminal double bonds. Importantly, the allylic oxidation of cyclohexenyl derivatives **4** was not only regioselective but highly diastereoselective, the *tert*-butanesulfinamide group being deeply involved in these selective processes.

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